
National Institute of Allergy and Infectious Diseases

BIODEFENSE WORKSHOP SUMMARY
MATHEMATICAL MODELS OF IMMUNITY: EXTPRAPOLATING HUMAN RESPONSES TO EMERGING INFECTIOUS DISEASES

June 10-11, 2003

Bethesda Marriott Hotel
Bethesda, Maryland

Overview

On June 10-11, 2003 the National Institute of Allergy and Infectious Diseases convened an expert panel of immunologists and mathematical modelers to advise on the state of the art and the scientific needs for development of mathematical models capable of simulating immune responses, directing novel experimentation, and generating a greater understanding of the immune system in infection, vaccination, and immune homeostasis. Participants provided overviews of several areas, including analysis of immune-based signaling events, B cell maturation, maintenance of immunological memory, and pathogen/host interactions. New methods for *in silico* analysis of cell signaling and behavior at various levels of resolution were also introduced. The panel concluded that mathematical modeling can make a significant contribution to identifying immunological principles that will lead to the development of improved vaccines and immunotherapeutics against infectious agents and immune-mediated diseases, and facilitate prediction of disease outcome and vaccination. Development of such mathematical models requires interdisciplinary teams with expertise in computer science, mathematics, immunological processes, and the technical capability to collect the quantitative information necessary for effective simulation. These teams would develop modeling tools that are validated and perfected through iterative rounds of simulation and laboratory experimentation, and after which these models would be distributed to the broader research community. Expert panel discussions revealed three critical areas that require support in order to advance the field. These areas include research, infrastructure, and education and training.

Recommendations

Research

1) Identify the fundamental goal of the model. Intermediate knowledge of the system may be adequate for some modeling; other goals will require more detailed information.

a) Higher order modeling may allow for less detailed understanding of the system to be modeled (abstractness), while still providing a great deal of important information. Example: cell dynamics in viral infections.

b) There is an ongoing need to fund "basic immunology" that provides detailed biological information required for development of useful models. Examples include:

i) Quantitation of the interactions: binding partners; mechanisms of binding; and kinetics.

ii) Development of new and expansion of current technologies to generate data for modeling (a lot can be done with current technologies, but more is needed); and make these technologies accessible to the community.

2) Base modeling efforts on systems that can be quantified.

a) Clearly define the parameters of questions to be addressed by the model for appropriate data collection.

b) Establish standards for generation and collection of immunologic data with input from the user community.

3) Interdisciplinary teams are critical for developing, improving, and validating mathematical models. Requirements include:

a) Teams of sufficient size and depth that include immunologists, physicists, mathematicians, engineers, microbiologists, statisticians, and epidemiologists.

b) Teams to work in close proximity with frequent interactions in a goal-oriented manner.

c) Development of methods to support "career" staff scientists as a vital resource for program maintenance/continuity.

4) Capability to extrapolate from animal studies to human; descriptive to predictive biology-based models.

a) Toxicological studies: evolution from descriptive, simple statistical approaches to compartment models, then to more elaborate physiologically based predictive studies (e.g., pharmacokinetic and pharmacodynamic).

b) Predictive studies have evolved from forecasting changes in a biological parameter to predicting dynamic responses and spatial orientation.

c) Allometric scaling: identify simple relationships that scale and those that do not scale among species (requires species specific information).

d) Parallelogram: collect experimental results from animal *in vivo* studies, animal *in vitro* studies, and human *in vitro* studies; use knowledge gained from these experiments to extrapolate to human *in vivo* response. This system requires development of platforms that accommodate various levels of resolution (cell, tissue, whole organism).

Infrastructure

1) Support required for development of systems to foster data sharing and cross-talk among researchers (e.g., BIRN – NCRR network for sharing imaging and other neurological data among Neuroscience Centers http://www.ncrr.nih.gov/biotech/btbirn.asp).

   a) Publicly accessible database of immunologic data (need to include methods for validating information within the database, may be as simple as including disclaimers or original sources of the information). The panel agreed that this is critical for development of robust models, because it allows for use of large data sets in model generation and validation.

   b) Biologist-friendly modeling/simulation tools: permits experimentalists to conduct computer simulations based on data-derived hypotheses without requiring direct input from outside mathematicians, then return to the bench to refine the model.

Efforts should be made to integrate or modify existing tools and systems that are commercially or publicly available, to the field of immunology

Education and Training: Critical to bring modeling into the 'mainstream" of immunology

1) Support concentrated training workshops (e.g., 6 weeks, NSF model) in mathematical modeling of immunity (could be included as a task within a Centers Program or as a separate initiative).

   a) Outcome goal for participants: To develop an appreciation for the power of mathematical treatment of immunological phenomenon, similar to what exists in the fields of population genetics, ecology, and epidemiology.

   b) Participants: students, post-doctoral fellows, and established researchers in the areas of engineering, mathematics, or immunology.

2) Incorporate modeling sessions into major immunology meetings as an approach to involve more immunologists in modeling by disseminating information about immune modeling "success stories. "

3) Support specific training programs (career (K) and department training (T) awards) in mathematical modeling of the immune system. The goal of these programs would be to foster an understanding of the power of mathematical models of immunological phenomena and the comprehension of the human immune response, similar to what exists in the fields of population genetics, ecology, and epidemiology.